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Abbreviations: MC, mast cell; nMC, nasal mast cell; pMC, pulmonary mast cell; EMC, intra-epithelial mast cell; LMC, lamina propria mast cell; MMC, mucosal type mast cell; CTMC, connective tissue type mast cell; AR, allergic rhinitis; MC_T, tryptase positive mast cell; MC_{TC}, tryptase and chymase positive mast cell; AR, allergic rhinitis.

Introduction

Since mast cells (MCs) are distributed almost throughout the whole body in health and are redistributed in different diseases, MCs may play an important role in health and diseases. However, their characteristics are different from species to species, and from organ to organ in the same species (1). Accordingly, in this article the author will focus only on the human airway (nose and lung) in normal, allergic and non-allergic diseases and clarify the similarity and differences between nasal MCs (nMCs) and pulmonary MCs (pMCs) from the point of view of MC heterogeneity.

Sampling of specimens

MCs are often collected by lavage, brushing or by tissue biopsies. Collecting specimens from the nose is easy. Nasal washings or suction of nasal secretions are often carried out without discomfort for the patients. However, there is a marked difference in cell populations between lavage fluid and tissue samples. The population of MCs is smaller in bronchoalveolar lavage (BAL) (2) and in nasal secretion (3) than in tissue samples, since MCs are predominantly cells residing in the tissue like lymphocytes, and unlike eosinophils and neutrophils. Consequently nasal and

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bronchial lavages are not fully representative for the study of MCs in the airways.

A nasal scraping can be used for the examination of intra-epithelial MCs (EMCs) but not for that of lamina propria MCs (LMCs). On the other hand, nasal biopsies are useful for studying MCs in the entire mucous membrane. However, local anesthesia often injures the epithelial layer and a small biopsy contains the epithelial layer and a small part of the subepithelial layer only. The author have used surgical material as large as 3–4 cm obtained under general anesthesia from patients who had had a turbinectomy performed. However, this type of material cannot be obtained from normal subjects.

Contrary to the nose, access to bronchial tissue is more difficult. The study of specimens obtained under bronchoscopy is often influenced by artifacts due to local anesthesia and intubation. Due to the risk of complications subjects to be examined are limited to normal persons, and patients with mild and intermittent asthma. Lavage fluid contains numerous macrophages and few MCs, which are different from the cell population in the tissue (3, 4), suggesting that a bronchial lavage is inadequate for the study of tissue MCs, as have been mentioned for nasal lavage. Bronchial brushing is available for the study of EMCs provided that the bronchoscopic procedure does not injure the epithelium. Bronchoscopy specimens are usually too small to characterize the mucosal pathology of the condition, and often the specimens are injured by pressure from the forceps. Large surgical materials are desirable but they can be obtained only during surgery or at autopsy. Dispersed cell system is similar to the standard chopped lung system in its dose–response relationship, kinetics and pharmacologic modulation (5). Thus, the lung fragment is used similarly as dispersed pulmonary cell specimens (pMCs).

The above-mentioned problems in sampling of specimens should be considered for the examination of MCs in individual organs and the comparison of nMCs with pMCs.

Identification of MCs

Histological and cytological specimens should be fixed in Mota's, Carnoy's, ethanol-acetic acid or IFAA solutions, but not in formaldehyde which blocks dye binding in toluidine blue staining (6). MCs are often stained with toluidine blue (pH 0.5 or 4.0), May–Grünwald–Giemsa or Hansel solutions, and the cells are identified by their metachromatic granules.

It is known that there are at least two types of MCs, i.e. mucosal type MCs (MMC) and connective tissue-type MCs

(CTMCs) on the basis of their location, morphology, staining properties, chemical content, response to chemical agents and drugs. The nomenclature of MC phenotypes is still controversial. In addition to MMCs and CTMCs, the terms tryptase-positive (MC_T) and tryptase and chymase-positive (MC_{TC}) or formalin-sensitive and resistant MCs are also used. In this article the terms MMCs and CTMCs will be used, which are almost synonymous to MC_T and MC_{TC} .

In histological and cytological studies MMCs are formalin-sensitive and CTMCs are formalin-resistant. In alcian blue-safranin staining MMCs stain blue and CTMCs red, and in berberin staining MMCs are negative and CTMCs are stained yellow.

In immunohistochemical studies monoclonal antibodies against anti-human IgE, anti-c-kit receptor (the ligand of stem cell factor), FcεRI and tryptase are often used for specific identification of both phenotypes of MCs, especially for activated mature MCs. However, cells having FcεRII such as lymphocytes, eosinophils and monocytes are often immunoreactive to anti-human IgE antibody.

Ultrastructurally, MCs are characterized by their specific endoplasmic granules. MMCs are smaller, oval or elongated in cell shape, rich in microvilli and have a smaller number of specific granules with fine granules of a uniform dark pattern, while CTMCs are larger, elongated or oval in shape, packed with numerous granules having a diverse pattern. They are fine, granular and contain scrolls and lamellae. When degranulated in allergic rhinitis, there is fusing of neighboring granules and cell membrane, resulting in the formation of labyrinths. The cells show part or total vacuolation (7) (Figs 1–3). Unlike rodent MCs, the escape of granules from the cell to the outside of the cell is not observed in human MCs in allergic rhinitis (AR).

In fixation and staining properties, immunohistochemical characteristics and ultrafine structure pMCs are similar to nMCs (8, 9). In the loose connective tissue and alveolar septa in the lung MCs are smaller, similar to nMMCs. In the lamina propria of bronchioles they are flattened, highly elongated and larger, similar to nCTMCs. The specific granular pattern in pMCs is complex with scrolls, lamellae and crystalloids (9).

Location of MC phenotypes in the airway

Both nMCs and pMCs occur in the entire layer of the airway mucosa. However, the population of phenotypes is varied depending upon the mucosal layer and disease involved. In AR approximately 90% of MCs in the epithelium has



Figure 1. Intra-epithelial nasal MMC with small size similar to leukocytes and small number of endoplasmic specific granules.

characteristics of MMCs, while that in the lamina propria has characteristics of CTMCs (10) (Table 1). This is similar in chronic sinusitis but different in non-allergic infective rhinitis, where there are no EMCs (11). In patients with Japanese cedar pollinosis EMCs are increased in-season but not out of season (12).

EMMCs are increased both in the pollen season and after allergen challenge (13–15), suggesting that EMMC play an important role in allergic rhinitis.

Irani et al. reviewed the population of MCs phenotypes in different tissues in a series of human organs. The majority of pMCs in the bronchial epithelium, bronchial subepithelium, alveoli and dispersed lungs cells are MMCs (16). However, the materials examined are mainly MCs from normal subjects or lung fragments but the phenotype of MCs in the lamina propria of bronchial tissue has not been examined. Bradding et al. studied the density of bronchial MC phenotypes in normal controls and asthma patients (17) (Table 2). In the normal bronchial epithelium MCs are almost nil, while in asthma the number is significantly increased with much more tryptase-positive MMCs than chymase and tryptase-positive CTMCs, as in AR.

Table 1. Distribution of basophil leukocytes and mast cell subsets in allergic rhinitis. The majority of MCs in the epithelium is of the MMC type and that in the lamina propria is of the CTMC type (from 11)

	Basophils (%)	MMCs (%)	CTMCs (%)
Intra-epithelial	2.4	90.3	7.3
Lamina propria			
Superficial layer	22.9	30.2	46.9
Deep layer	4.1	10.9	84.9

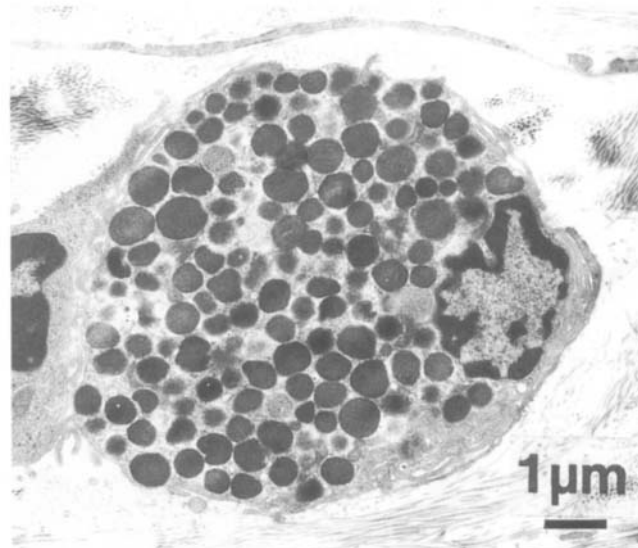


Figure 2. Lamina propria nasal CTMC with larger size and numerous number of specific granules.

Furthermore, the submucosal tryptase-positive cells are the same in normal controls and in allergic asthma, while there are more chymase and tryptase-positive cells in asthma than in normal controls, indicating an increase of CTMCs in the submucosa in asthma (Table 3), which is similar to AR.

Based on these results it can be concluded that MMCs are increased in the epithelial compartment and CTMCs in the lamina propria in asthma and in AR.

Chemical contents in MCs (Tables 4 and 5)

MCs contain different kinds of chemical mediators and cytokines, and they release them in allergic and non-allergic reactions together with newly generated mediators from the cell membrane, resulting in inflammatory tissue reactions.

Histamine, a major mediator in the allergic reaction, is localized in the specific granules, and the total amount per MMC is lesser than that in CTMC, as the number of specific granule is lower in the MMCs. This applies both to nMCs and pMCs. However, the percentual histamine release is higher in EMMC than in LMCs, suggesting that EMMC are more activated than LMCs. Histamine has many effects such as bronchoconstriction, tissue edema, mucus secretion and fibroblast proliferation (18).

MCs in the nose and lung contain neutral proteases which differ according to the phenotype (16, 18–21). Tryptase (trypsin-like protease) and chymase (chymotrypsin-like protease) are commonly contained in nMCs and pMCs.

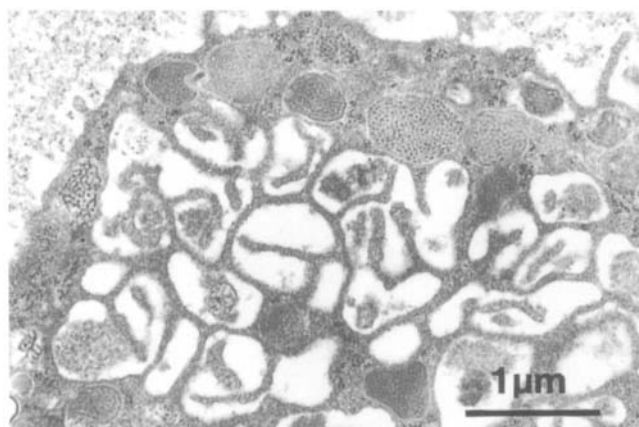


Figure 3. Degranulated MMC with labyrinth formation by fusion of vacuolated specific granules.

However, MMCs have mainly tryptase and CTMCs have mainly chymase but also tryptase. Bronchial and lung MCs contain much more tryptase than chymase [19]. Tryptase exerts different functions: 1) cleavage of the bronchodilator peptides, 2) peptide histidine methionine, and vasodilator calcitonin gene-related peptide; 3) sensitization of bronchial smooth muscle to contractile agents; 4) a kallikrein-like activity, which cleavages the matrix; 5) mitogenic activity for fibroblasts and epithelial cells; 6) stimulation of release of the granulocyte chemoattractant IL-8; and 7) upregulation of ICAM-1 expression on epithelial cells [19].

Church et al. have suggested the following functions of chymase: 1) degradation of the neuropeptide neurotensin; 2) cleavage of angiotensin I to angiotensin II; 3) cleavage of type IV collagen and splitting of the dermal-epidermal junction; 4) conversion of IL-1 β to IL-1; 5) degradation of IL-4; and 6) stimulation of secretion from gland cells [18].

With regard to proteoglycans, both nMMCs and pMMCs contain much more chondroitin sulfate E than heparin, while both nCTMCs and pCTMCs have much more heparin than chondroitin sulfate [21–23].

Church et al. also suggested that proteoglycan may affect the stability and function of other MCs mediators, i.e. heparin stabilizes the active tetramer of tryptase; other actions include anticoagulant, anti-complement, and anti-kallikrein effects, the ability to sequester eosinophil major basic protein, enhancement of collagen binding to fibronectin and numerous growth factor-enhancing activities [18].

Recently, it has been demonstrated that MCs contain different kinds of cytokines with an effect on lymphocytes, epithelial cells, macrophages and eosinophils, suggesting a versatile role of MCs not only in the acute allergic reaction but also in chronic allergic reactions and in local IgE synthesis [17, 24, 26] (Fig. 4).

Table 2. Percentual distribution of mast cell subsets (from 17)

Tissue location	MC _T	MC _{TC}
Skin	12	88
Lung		
Bronchial epithelium	99	1
Bronchial subepithelium	77	23
Alveoli	93	7
Dispersed lung cells	90	10
Small intestine		
Mucosa	98	2
Submucosa	13	87
Nose		
Epithelium	100	0
Subepithelium	60	40
Conjunctiva		
Epithelium	100	0
Subepithelium	20	80

MC_T = mast cells with tryptase, corresponding to MMCs. MC_{TC} = mast cells with tryptase and chymase, corresponding to CTMCs.

Bradding et al. reported that in both the upper and lower airways of normal subjects and patients with allergic diseases, IL-4 is localized to both phenotypes of MCs, but predominantly to CTMCs, while IL-5 and IL-6 are localized almost exclusively to MMCs [17, 24, 25] (Table 3). However, other studies have indicated that the proportion of IL-4 is predominant in the lamina propria nMCs, while IL-5, IL-6 and IL-13 are not much different between epithelium and lamina propria MCs [26].

Reactions to chemical agents (Tables 4 and 5)

The different MC subsets react differently to chemical agents. Both phenotypes of nMCs and pMCs degranulate and release chemical mediators upon contact with calcium ionophore and the agent A-23187 [27–29].

Substance P, a neurotransmitter, is proposed to cause MC degranulation. However, unlike the skin CTMCs, both phenotypes of airway MCs do not give a concentration-dependent release of histamine in response to substance P, suggesting that substance P does not potentiate neurogenic inflammation in the allergic reaction in the airways [28–30].

Table 3. Mast cell subsets and cytokine distribution in the mast cell phenotypes in normal subjects and in asthma. Cell counts (median) in the bronchial mucosa expressed as cells/mm² of epithelium and cells/mm² of submucosa (from 17). While IL-4⁺ cells were present in both epithelium and submucosa, IL-5⁺ and IL-6⁺ cells were restricted to the submucosa

	Epithelium		Submucosa	
	Normal	Asthma	Normal	Asthma
Tryptase	0	2.2	46.3	61.5
Chymase	0	0.7	12.3	34.6
IL-4 (3H4)*	0	1.3	3.2	50.0
IL-4 (4D9)*	0	0	14.8	7.7
IL-5	0	0	8.4	5.1
IL-6	0	0	16.8	6.6

* Two kinds of antibody to IL-4.

Compound 48/80 is known to release mediators from rat peritoneal MCs but not from the intestine MCs of mucosal type [31]. On the other hand, human airway MCs of both phenotypes are insensitive to this agent [27, 28].

Kinin is also proposed to activate tissue MCs and release histamine from rat MCs. However, human pMCs are totally unresponsive to kinins. Any role for bradykinin in asthma and AR is therefore unlikely to involve MC activation [32].

Reactions to drugs (Tables 4 and 5)

The heterogeneity of MCs in the reaction to pharmaceutical compounds is important for the treatment of airway allergy.

Sodium cromoglycate (cromolyn sodium) introduced a new concept of MC stabilizers for the treatment of airway allergy. This concept was based mainly on animal experiments using rat CTMCs. However, later Pearce et al. revealed that MMCs of the rat intestine are insensitive to cromoglycate with regard to inhibition of chemical release of mediators [33]. The author also demonstrated that human nMMCs are only weakly sensitive and nasal and pharyngeal CTMCs are moderately sensitive to sodium cromoglycate [34]. Okyama et al. also revealed that a high concentration of this drug significantly inhibited histamine release from pMCs [35].

The inhibitory effect of antihistamine on mediator release from MCs are also heterogeneous. Some H₁ antihistamines inhibit MC mediator release at low concentrations, while at high concentrations they increase histamine release [36].

Table 4. Characteristics of mast cell phenotypes

	MMCs	CTMCs
Morphology		
Size	Small	Large
Shape	Round/elongated	Oval/elongated
Specific granules and lamella	Few, granular	Many, scrolls
Staining properties		
Alcian blue, safranin	Blue	Red
Berbeline	Negative	Yellow
Formalin fixation	Staining blocked	Staining not blocked
Carnoy, Mota fixation	Staining not blocked	Staining not blocked
Localization	Epithelium	Lamina propria
Chemical content		
Neutral proteases	Tryptase	Tryptase and chymase
Proteoglycans	Chondroitin sulphate	Heparin
Histamine	Low (< 2 pg/cell)	High (< 35 pg/cell)
Cytokines	IL-4, 5, 6, 13 TNF- α , GM-CSF, SCF	The same
Life span	Short	Long
Local IgE synthesis	Not involved	Involved
Role in allergy	Acute response	Chronic, remodeling
Fibrosis	Not involved	Involved
Effect of chemical compounds and drugs on mediator release		
A 23187	Sensitive	Sensitive
Compound 48/80	No effect	No effect
Substance P	No effect	No effect
Cromoglycate/ Nedocromil	Weak effect	Moderate effect
Many new H ₁ blockers	Effect	Effect
Topical corticosteroid	Effect on cell number	No effect
Immunotherapy	Effect on cell number	No effect

Recently it has been reported that new H₁ blockers such as ketotifen, terfenadine, azelastine and loratadine inhibit mediator release from pMCs [37, 38], and terfenadine inhibits histamine release from both types of nMCs [39] (Fig. 5). These effects are not unrelated to their ability to antagonize histamine at the H₁ receptor site. Accordingly it is presumed that, as a mode of action, H₁ blockers may directly interact with the MC membrane to stabilize it

Table 5. Characteristics of human mast cells in the lower airways

	Bronchi	Lung
Localization		
Epithelium	MMC > CTMC	MMC > CTMC
Submucosa	MMC < CTMC	
Chemical content		
Protease	Tryptase > chymase	Tryptase > chymase
Proteoglycan	ND	Condroitin > heparin
Histamine	Low-content-cells > high-content-cells	Low-content-cells > high-content-cells
Cytokines	IL-4, IL-5, IL-6, IL-13 TNF- α , GM-CSF	IL-4, IL-5, IL-6, IL-13 TNF- α , GM-CSF
Reaction to antigen	Release of histamine PGs, LTs	Release of histamine PGs, LTs
A-23187	Sensitive	Sensitive
compound 48/80	ND	not sensitive
substance P	ND	not sensitive
kinin	ND	Not sensitive
cromoglycate	ND	No/weak inhibition
terfenadine	ND	Sensitive
corticosteroid	ND	Sensitive (MMC only)
IgE synthesis	ND	Implicated (CTMC only)
Role in allergy	MMC in acute phase CTMC in chronic phase	MMC in acute phase CTMC in chronic phase
Fibrosis	ND	Implicated (CTMC only)

since, due to their lipophilic cationic nature, they dissolve into the cell membrane at low concentration (40).

Corticosteroids are very potent and effective in the treatment of airway allergy. The use of systemic corticosteroids is restricted due to the well-known side effects. Topical steroid compounds such as beclomethasone dipropionate, flunisolide, budesonide and fluticasone propionate are used widely because of their high efficacy and minimum side effect. They have diverse anti-inflammatory effects but the mode of action on MC phenotypes is not still fully understood.

Topical steroids reduce the number of nMMCs in the epithelium (41) (Table 6), and many studies have shown that a migration of nMMCs to the mucosal surface is inhibited by topical steroid following exposure to allergen (43, 44). The LMCs are not suppressed (42, 45, 46). In other words, corticosteroids affect nMMCs but not nCTMCs.

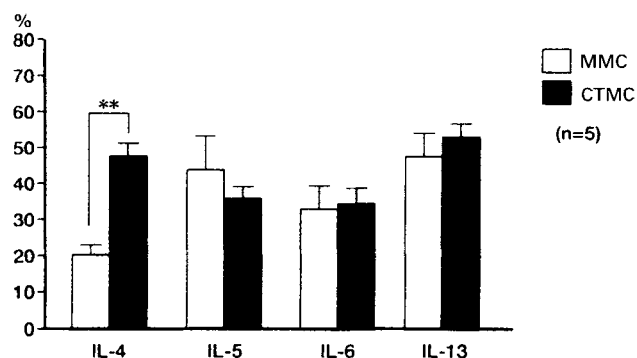
Relative amount of cytokines expressed by MMCs and by CTMCs

Figure 4. Cytokine profile of MC phenotypes. The proportion of cytokine IL-4 is predominant in the epithelium (MMC rich) but IL-5, IL-6 and IL-13 are not different between both layers (MMC and CTMC) (26).

Corticosteroids may exert their function by modifying the inflammatory process, i.e. inhibiting leukocyte priming, reducing the secretion of cytokines and other mediators and modulating enzyme systems, migration of MCs, lymphocytes and eosinophils, and finally by decreasing the permeability of blood vessels and edema formation (47). Among the above-mentioned factors the decreased number of MMCs may be a very important part of the anti-inflammatory activity of corticosteroids in allergic disease.

Immunotherapy is known to be effective in the treatment of airway allergy. However, the mode of action needs further studies. The theories of blocking antibody and reduction of serum specific IgE antibody levels may be outdated, since the symptoms do not correlate with the changes of these parameters after immunotherapy. Instead of these theories, the correction of immunodeviation from Th1 to Th2 is now

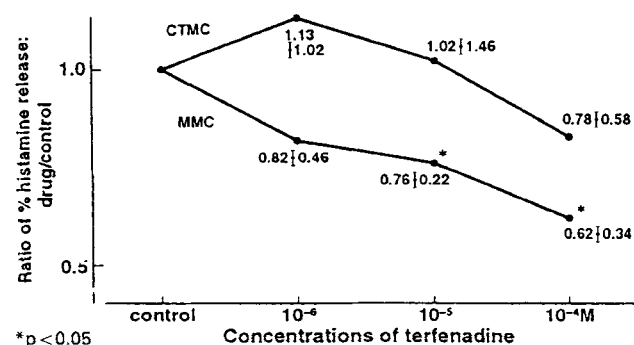
Inhibitory effect of terfenadine on *in vitro* allergen induced histamine release from CTMCs and MMCs

Figure 5. Inhibitor effect of terfenadine, a non-sedative H₁ blocker, on allergen-induced histamine release from subtypes of MCs. Both phenotypes are sensitive to the drug (39).

Table 6. Changes in test results during treatment with beclomethasone dipropionate (BDP) (41)

	<i>n</i>	Increased	Unchanged	Decreased	<i>P</i>
Symptom severity					<0.01
Control	23	2	19	2	
BDP	27	2	11	14	
Antigen provocation					<0.01
Control	21	2	13	6	
BDP	27	1	7	19	
Basophilic cells count					<0.01
Control	25	5	15	5	
BDP	28	1	9	18	
Histamine provocation					NS
Control	16	0	16	0	
BDP	25	1	24	0	

a more likely hypothesis (48, 49). The author previously showed a decrease in the number of EMCs after immunotherapy for 6 months in AR, and the reduction in the cell count correlated positively with the degree of symptom reduction (50). The number of LMCs was unchanged. Recently, we observed a relative increase in IFN- γ positive Th cells and a relative decrease in IL-4 positive Th cells during immunotherapy in patients with Japanese cedar pollinosis (unpublished observations). As far as we know there is no such study on the effect of immunotherapy on pMCs in asthma patients.

Specific IgE synthesis by MCs without HLA restriction

Basically antibody production is conducted by the contact of Th cells with B cells in MHC restricted conditions. However, it has been revealed recently that this synthesis can occur by the binding of CD40 ligand of activated Th cells or other cells with CD40 of B cells without MHC restriction.

Gauchat et al. first demonstrated that in the presence of IL-4, PMA and anti-CD40L, MC and basophil cell lines can provide the cell contact signal that are required for IgE synthesis and they showed that purified pMCs also express CD40L and induce IgE production independently of T cells (51). In this context, Pawankar et al. recently reported increased expression of CD40L in nMCs and the release of IL-4 and IL-13 on contact of MCs with specific antigen, and then demonstrated specific IgE antibody production after incubation of activated MCs with tonsillar B cells from non-

atopic persons (52). This IgE production was antigen specific and blocked by pretreatment with monoclonal antibodies against IL-4, IL-13 or CD40L. In addition, they also demonstrated that nMCs of patients with allergic rhinitis had upregulated Fc ϵ RI (52, 53).

B cells in the nasal mucosa are found to be around 20% of total lymphocytes in the allergic nasal mucosa (54), but IgE-bearing cells are very few in contrast to IgA-bearing cells (55) and the majority of IgE positive cells are MCs and not B cells, which are rare (56).

Thus, although MC-induced, non-MHC restricted IgE synthesis is an attractive model, it seems to be questionable whether IgE antibody synthesized in the nasal mucosa is supplied to the circulation. However, since the progenitor MCs, released from the bone marrow, enter into circulation and mature and proliferate at local sites (57), minute amounts of IgE antibody from a small number of B cells may be sufficient to sensitize MCs together with IgE antibody in the tissue fluid. Since there is no B cell in the epithelial compartment (54), this type of IgE production may be conducted by CTMCs in the lamina propria. This different function is due to different location but not due to the heterogeneity in MC characteristics

Role of MC heterogeneity in acute allergic reaction (Fig. 6)

The allergic reaction is triggered by cross-linking of antigen-specific IgE antibody with the high affinity IgE receptor (Fc ϵ RI) on the surface of MCs, resulting in the aggregation of

FcεRI. This aggregation induces the activation of intracellular enzyme systems which results in the release of preformed chemical mediators such as histamine, chemoattractants, proteoglycans, neutral protease and Th₂ type cytokines, as well as newly generated mediators such as leukotrienes, prostaglandins and PAF.

Allergic airway manifestations occur mainly by reflex stimulation of the major mediator, histamine, on sensory nerve endings (sneezing and runny nose) and by direct action of histamine and leukotrienes on the blood vessels (onset of stuffy nose due to congestion and edema) (58).

Evidence in support of the important role of MMCs in the acute allergic reaction are accumulated. As is already mentioned, numerous numbers of MMCs gather in the epithelial compartment in airway allergy. After allergen challenge the ratio between degranulated granules and total

number of granules in EMCs is increased markedly but not that of LMCs, suggesting a central role of EMCs in triggering the acute allergic reaction (59) (Table 7). The number of EMCs with full degranulation in the bronchial wall is higher in asthma than in normal controls, and LMCs with full degranulation are markedly less than EMCs (60) (Table 8).

After allergen challenge or natural exposure to allergen many different kinds of MC-derived bioactive substances, as mentioned above, are increased in the nasal secretion (61–63). Of chemical mediators, histamine and leukotrienes are the most important for the acute allergic reaction in the nose, since both mediators are released in considerable amounts following allergen challenge, and they can both induce allergy-like nasal symptoms by provocation, and this reaction can be blocked by their specific antagonists. In addition, unilateral nasal allergen provocation increases the mediators in nasal fluid to a higher degree on the provoked side than on the contralateral side (64).

The number of EMCs and their histamine releasability are well correlated with the degree of symptoms in allergen challenge (65).

In the lower airways, segmental bronchial allergen challenge causes the release of mediators, such as histamine, LTC₄ and PGD₂ (66–68).

Role of MC heterogeneity in chronic allergic reactions (Fig. 7)

Following or after an interval of the acute allergic reaction, late phase responses often occur with exudation, edema formation, inflammatory cell migration and secretion. The mechanisms and clinical significance are still not fully understood. Bentley et al. have reviewed the dynamics of MCs after allergen challenge. Decrease as a consequence of degranulation and loss of granule staining in BAL is observed, while increase is seen in bronchial biopsy. On the other hand, no significant change in MC numbers between pMMCs and pCTMCs exists (69–71). Since EMCs are migratory cells, MMCs in the epithelium may increase after acute reaction (72).

Recently, cytokine release from MCs have provided a new understanding of the late phase reaction. In addition to chemoattractants such as PAF and LTB₄ released from MCs in the acute phase, different cytokines may play an important role in inflammatory cell migration at local sites, resulting in tissue stimulation and damage by mediators released from degranulation of the inflammatory cells.

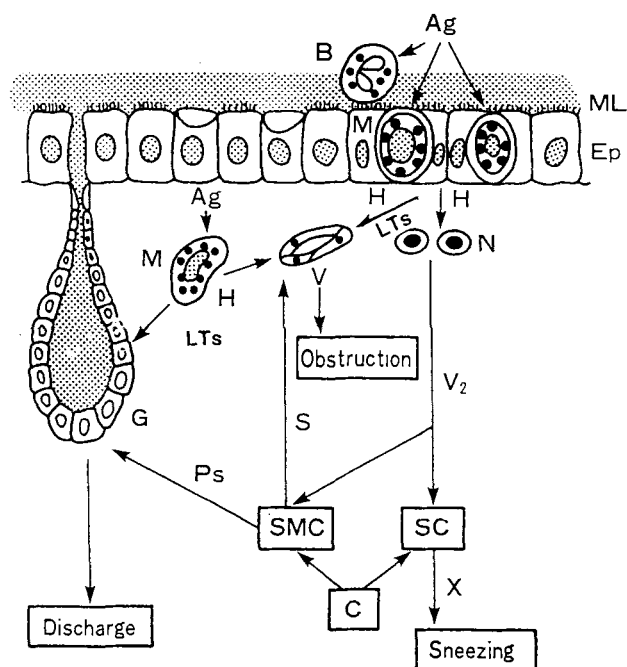


Figure 6. Mechanism of the acute allergic reaction. Allergen inhaled and deposited on the nasal mucosal surface elutes allergenic substance in the mucus blanket. On contact of the allergen with surface MMCs and basophils preformed and newly generated chemical mediators are released from these cells. Histamine induces sneezing and secretion by a reflex via sensory nerves, the sneezing centre and secreto-vasomotor centers and efferent parasympathetic pathways, and leukotrienes and histamine cause stuffy nose, namely congestion and tissue edema by their direct actions on the blood vessels. MCs in the lamina propria, lining epithelial cells, autonomic nerve system and neuropeptides also contribute to this allergic reaction (57). Ag=antigen; B=basophil leukocyte; M=mast cell, ML=mucous layer; Ep=epithelium; H=histamine; LTs=leukotrienes; N=nerve ending; V=blood vessel; G=secretory gland; V₂=maxillary nerve; X=vagus nerve; S=sympathetic nerve; Ps=parasympathetic nerve; SMC=secreto-motor center; SC=sneeze center; C=superior center.

Table 7. Changes in the degree of degranulation in nasal mast cells after allergen provocation

Site	Provocation	Number of MCs	Number of granules	Degree of degranulation*
Epithelial layer	before	69	2125	31.3%**
	after	59	1244	69.3%**
Lamina propria				
superficial layer	before	43	1582	39.0%
	after	32	717	30.0%
Lamina propria				
deep layer	before	64	2817	24.2%
	after	47	1574	23.6%

* Number of degranulated granules per total number of granules; ** $P<0.01$.

It is now known that IL-4, IL-13 and TNF- α can upregulate adhesion molecules such as VCAM-1 and ICAM-1 expression in the endothelial cells (73). Since these are released from MCs on contact with allergen, MCs may contribute to the recruitment of eosinophils and basophils through the upregulated adhesion molecules for the late phase response (74, 75). There is not only expression of adhesion molecules, but also release of IL-4 from MCs, which activates Th2 cells resulting in enhancement of IL-5 release and increase and longer survival of eosinophils (76). Both phenotypes of MCs can release these cytokines but since EMCs may initially contact with allergen due to their location, and, if IL-5 is localized exclusively to MMCs, EMCs may be more important than LMCs to attract eosinophils together with other attractants such as RANTES, eotaxin and monocyte chemotactic protein (MCP) from epithelial cells.

Table 8. Distribution of mast cell subtypes (cells/mm²) in the epithelium and lamina propria of the bronchial wall after staining with toluidine blue (60). The number of MCs and the number of degranulated cells in the epithelium are higher in asthma patients than in normal controls. In the lamina propria, the total number of MCs is similar in the two groups, but in asthma there is an increased percentage of cells that are degranulated. These observations suggest that EMCs play an important role in asthma, as in allergic rhinitis

Number (percentage)	Asthma	Normal control
Epithelium		
Degranulated	21.0 (78.7%)	3.9 (55.7%)
Partly degranulated	5.7 (21.3%)	3.1 (44.3%)
Fully granulated	0 (0%)	0 (0%)
Lamina propria		
Degranulated	17.3 (23.0%)	3.0 (4.2%)
Partly degranulated	40.6 (54.2%)	23.1 (32.4%)
Fully granulated	17.0 (22.7%)	45.2 (63.4%)

It is believed that asthma is characterized by eosinophilia and epithelial damage by cationic proteins being released from eosinophils. However, in AR, in spite of massive eosinophilia, there is no evidence of tissue damage by eosinophils. The epithelial cells are well preserved and mucociliary transportation is normal, and the degree of clinical symptoms and hyperreactivity to histamine are not significantly correlated with the degree of eosinophilia (77).

Role of MC heterogeneity in fibrosis

Repeated allergic reactions cause fibrosis as a repairing process of tissue damage in the airway mucosa. MCs do not seem to be essential for the development of fibrosis but may play a role in this regard along with other inflammatory cells, since MCs usually are found in fibrotic lesions.

Choi et al. reviewed the contribution of MC content to the process of fibrosis (78). Histamine can stimulate fibroblast growth and collagen synthesis *in vitro* and *in vivo*. Heparin influences maturation of collagen fibers. Proteolytic enzymes activate procollagenase, which is a mitogen and comitogen for fibroblasts, and they also cleave extracellular matrix and glycocalyx. In addition, TNF- α , a cytokine from MCs, can stimulate the proliferation of normal diploid fibroblast, collagenase and prostaglandin E₂ production by normal human fibroblasts.

CTMCs in the lamina propria are increased both in allergic and in nonallergic nasal mucosa, suggesting that this increase is not specific for allergy but common in chronic inflammation (11). However, increased CTMCs in AR are different in immunological characteristics from those in nonallergic infective rhinitis with regard to expression of Fc ϵ RI, and immunological release of chemical

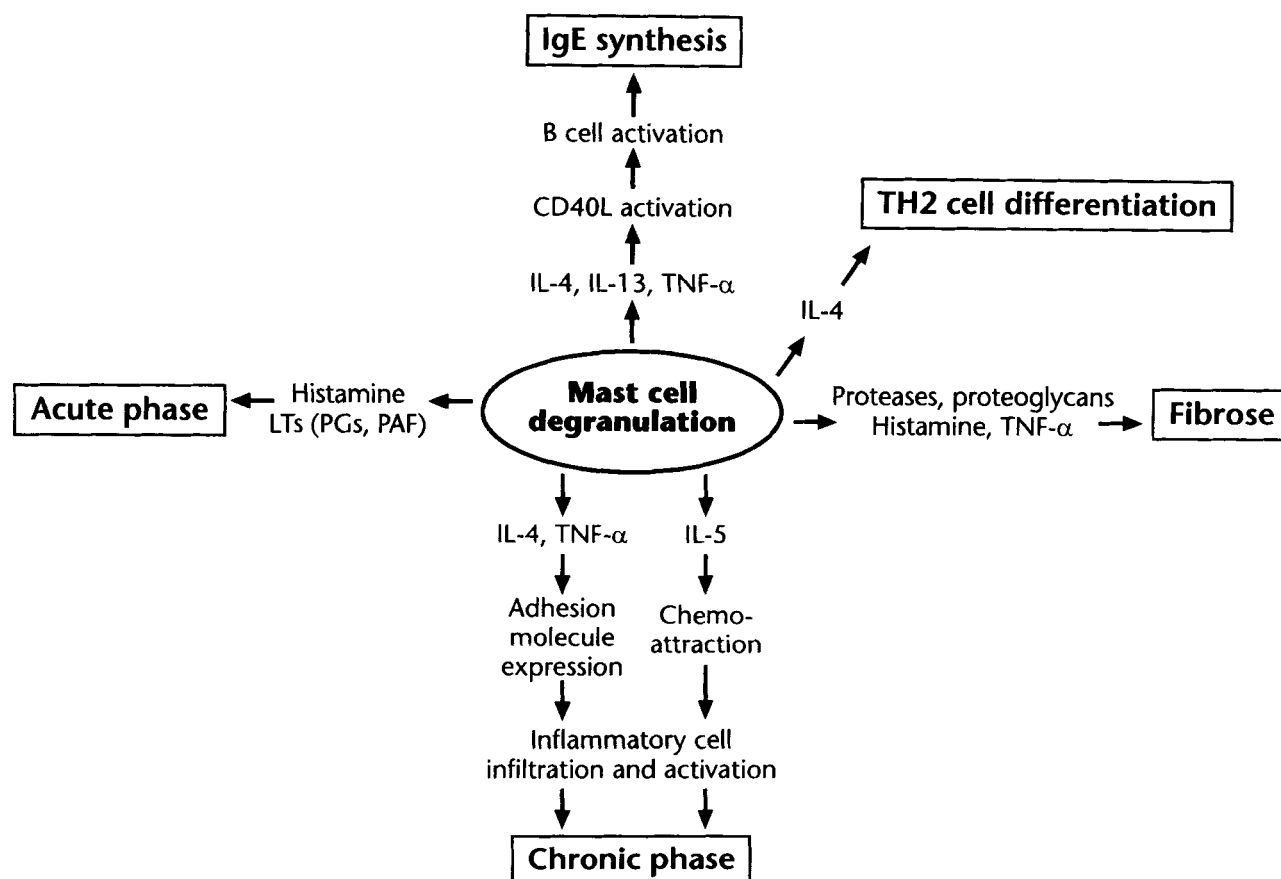


Figure 7. Overview of acute and late-phase allergic reaction in the airway on the basis of a hypothesis that MCs play a central role in this reaction. MMCs contribute mainly to induce the acute reaction. On the other hand, CTMCs are involved mainly in the chronic reaction by inflammatory cells releasing cytokines and mediators for upregulated expression of adhesion molecules on endothelial cells, and production of chemoattractants. Consequently, these cells may cause the release of inflammatory factors which are involved in edema, hypersecretion and congestion. After repeated attacks and long duration of the inflammatory process, fibrosis may occur for repairing the damaged tissue. MCs in the lamina propria may play an important role in the fibrosis by releasing proteases, proteoglycan, histamine and TNF- α . In addition, specific IgE antibody may be produced mainly by MCs in the lamina propria by the interaction of upregulated expression of MC CD40L with B cell CD40 and sensitize MC during the process of maturation of local progenitor MCs.

mediators and cytokines [52]. Both sensitized and nonsensitized MCs in different pathological conditions may promote fibrosis.

Goto et al. demonstrated that in experimental bleomycin-induced pulmonary fibrosis of rats, only CTMCs (formalin-resistant MCs) increase in the lung [79] (Fig. 8). Both types of MCs have the potential for enhancing fibrosis. Due to their location CTMCs may be involved in the repairing process of the pathological allergic mucosa.

Thickening of the basement membrane is often seen in asthma [80] as well as in AR. The thickened basement membrane consists of proliferation of collagen fibers or fibrils covered with a gel of collagen types I, III and V. The basement membrane becomes swollen by infiltration with plasma exudate and it looks like a barrier against the penetration of inhaled foreign allergenic substances in

allergy. EMCs may be involved in the production of this barrier.

Conclusions

The author has reviewed human MCs in the nose and the lungs from the point of view of functional heterogeneity. The majority of MCs are MMCs in the epithelium of airways and lung fragments, and CTMCs in the lamina propria of airways. Both phenotypes are unresponsive to substance P, suggesting that MCs do not potentiate neurogenic inflammation in the airway by their degranulation.

MMC are weakly sensitive to sodium cromoglycate in inhibition of mediator release, and both phenotypes are

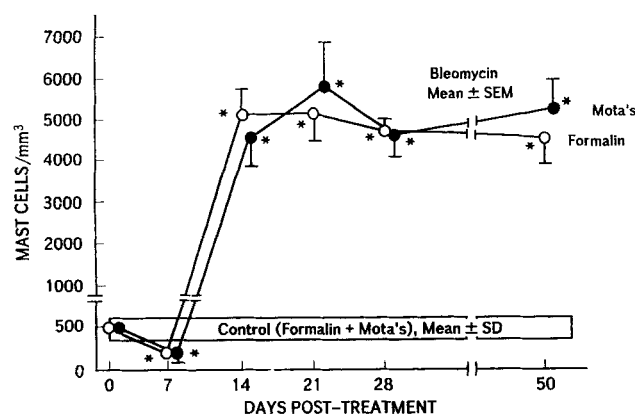


Figure 8. Effects of intratracheal bleomycin treatment on rat MC density in lung parenchyma indicating that the differences in MC number from control rats are significant and increased MCs are CTMCs since there is no difference in the number counted between fixation with Mota's and formalin solution [79].

inhibited by some H_1 -blockers, only at high concentrations. MMCs, but not CTMCs, are reduced in number by topical corticosteroid treatment and by immunotherapy. These

heterogeneities of MC phenotypes in response to pharmacological compounds should be considered for the treatment of allergic disease.

Local IgE synthesis is still not completely clarified. Interaction of CD40L of activated MCs with CD40 of B cells can produce IgE antibody without MHC restriction and T cell-B cell interaction. This system may sensitize MCs, which arrive as progenitor cells from the bone marrow and are matured and sensitized in the airway.

MMC's in the airway epithelium trigger acute allergic reactions by releasing chemical mediators, especially histamine and leukotrienes. In addition to chemotactic factors, released during the immediate phase, CTMCs may release cytokines which upregulates adhesion molecule expression in the endothelium and then induce the migration of inflammatory cells to the airways, resulting in chronic inflammation in the allergic airways.

After repeated allergic reactions repairing processes may progress to mucosal damage, and CTMCs in the lamina propria may contribute to this process.

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